The Resurgence of Sexually Transmitted Diseases

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Global STIs

- > 1 Million STIs are acquired every day globally
- Each year, an estimated 357 million new infections occur among 4 curable STIs
- > 500 Million people are estimated to have genital HSV
- > 290 Million women have HPV infection
- > 900,000 pregnant women infected with syphilis resulting in 350,000 adverse birth outcomes
- Drug resistance, especially for gonorrhea is increasing
Global Incidence of 4 Selected Curable STIs

- 131 Million C. trachomatis
- 78 Million N. gonorrhoeae
- 5.6 Million Syphilis
- 143 Million T. vaginalis
STDs in the US

• > 20 million new STDs in the U.S. annually
• >2 million cases of the three nationally reported STDs – chlamydia, gonorrhea, and syphilis – were reported in the U.S. in 2016, highest number ever.
• More than half of persons who contract STDs are under age 25
• All STDs have significant health disparity issues with rates often 10 times higher in Blacks
• STDs increase the risk of acquiring HIV
• The costs associated with these STDs are increasing:
  >US $16 Billion Annually; Funding for screening declining
US Estimates of Sexually Transmitted Infections

- Syphilis: 32,000
- HIV: 56,300
- Hepatitis B Virus: 73,000
- Gonorrhea: 700,000
- Chlamydia: 3.5 million
- Herpes Simplex Virus: 1.5 million (?)
- Human Papilloma Virus: 6.2 Million
- Trichomoniasis: 7.2 million
Newly Recognized STIs

• Ebola and Marburg Filoviruses: Virus is detectable in semen for 82 days and RNA > 13 months; Immunologic privileged sites/sanctuary

• Zika: 17 studies documenting sexual transmission and virus detectable in semen over 180 days
Ebola virus has lurked in a man’s semen for more than 500 days

By Debora MacKenzie

The Ebola virus can persist in a man’s semen for much longer than we thought. A man in Guinea who survived Ebola in 2014 is now known to have carried it for at least 531 days. Earlier this year, he transmitted the virus sexually, causing it to spread to at least 10 people, and killing 8 of them.
Results on RT-PCR in Semen Specimens from Survivors of Ebola Virus Disease

Prevention of Sexual Transmission of Ebola

- Men who have recovered from Ebola should abstain from sex for a minimum of three months if not longer.

- If abstinence is not possible then condoms should be used.
Transmission of Zika Virus Through Sexual Contact with Travelers to Areas of Ongoing Transmission — Continental United States, 2016

- 5 confirmed sexually transmitted cases in the U.S.
- 10 countries have reported probable sexually transmitted cases (WHO, 6/30/16)
# Recommendations: Couples Trying to Conceive

<table>
<thead>
<tr>
<th>Suggested timeframes to wait before trying to get pregnant</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traveled to an area with Zika or sex with a man who has been in an area with Zika</strong></td>
<td>Use condoms or abstain after symptoms start:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>at least <strong>8 weeks</strong></td>
<td>at least <strong>6 months</strong></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Use condoms or abstain:</td>
<td></td>
</tr>
<tr>
<td><strong>No symptoms</strong></td>
<td>at least <strong>8 weeks</strong></td>
<td>at least <strong>8 weeks</strong></td>
</tr>
<tr>
<td></td>
<td>Talk to doctor or healthcare provider</td>
<td></td>
</tr>
<tr>
<td><strong>Living in area with Zika</strong></td>
<td>Use condoms or abstain after symptoms start:</td>
<td></td>
</tr>
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<td>at least <strong>8 weeks</strong></td>
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</tr>
<tr>
<td><strong>No symptoms</strong></td>
<td>Talk to doctor or healthcare provider</td>
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</tr>
</tbody>
</table>

# Clinical syndromes: Common STIs

<table>
<thead>
<tr>
<th>Urethritis/ Cervicitis</th>
<th>Genital Ulcer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gonorrhea (GC)</td>
<td>• Syphilis</td>
</tr>
<tr>
<td>• Chlamydia (CT)</td>
<td>• Herpes</td>
</tr>
<tr>
<td>• (Mycoplasma genitalium)</td>
<td>• LGV, Chanchroid, Granuloma Inguinale</td>
</tr>
</tbody>
</table>

**Proctitis**
- GC, CT (also LGV proctitis), HSV, Syphilis

**Pharyngitis**
- GC

**Conjunctivitis:**
- GC, CT

**Vaginitis**
- Trichomonas
- Bacterial Vaginosis

**Skin lesions**
- HPV-warts, cancer
- Herpes
Overview of Complications of Sexually Transmitted Diseases

Infertility
Ectopic Pregnancy
Chronic Pelvic Pain

STDs

Upper tract infection
Systemic Infection

HIV infection
Congenital Infection

Fetal Wastage
Low Birth Weight
Cervical Cancer

Rate (per 100,000 population)

Year


Men

Women

Total
Epidemiology: *Chlamydia trachomatis*

- 89 million annual new cases worldwide
- 3.5 million new cases in U.S./year
- Most frequently reported STD in U.S.
- High prevalence co-infection in partners (>50%)
- Perinatal transmission can result in neonatal conjunctivitis and pneumonia in newborn infants
- Untreated infections increase risk for sequelae (PID, infertility, ectopic pregnancy, chronic pelvic pain)
Chlamydia — Rates of Reported Cases by Age Group and Sex, United States, 2016

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Men Rate (per 100,000 population)</th>
<th>Women Rate (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>12.7</td>
<td>91.1</td>
</tr>
<tr>
<td>10-14</td>
<td>832.6</td>
<td>3070.9</td>
</tr>
<tr>
<td>15-19</td>
<td>1558.6</td>
<td>3779.0</td>
</tr>
<tr>
<td>20-24</td>
<td>1003.4</td>
<td>1657.8</td>
</tr>
<tr>
<td>25-29</td>
<td>538.0</td>
<td>688.2</td>
</tr>
<tr>
<td>30-34</td>
<td>311.3</td>
<td>341.8</td>
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<tr>
<td>35-39</td>
<td>167.3</td>
<td>154.2</td>
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<tr>
<td>40-44</td>
<td>91.9</td>
<td>57.9</td>
</tr>
<tr>
<td>45-54</td>
<td>30.1</td>
<td>15.8</td>
</tr>
<tr>
<td>55-64</td>
<td>5.5</td>
<td>2.2</td>
</tr>
<tr>
<td>65+</td>
<td>330.5</td>
<td>657.3</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Chlamydia trachomatis

- Gram negative obligate intracellular bacteria
- Complex developmental biology modulates between infectious elementary body (EB) and non-infectious reticulate body (RB)
- Strict human pathogen
- Mucosal epithelial cell infection tropism
- Nonhuman primates only relevant infection and disease model
Chlamydia trachomatis
Chlamydia trachomatis

**MEN**
- Asymptomatic
- Urethritis
- Epididymitis (70% of cases in young men)
- Proctitis
- Conjunctivitis
- Pharyngitis (rare)
- Reactive arthritis (urethritis, conjunctivitis, arthritis, skin lesions)

**WOMEN**
- Asymptomatic
- Cervicitis
- Urethritis
- Pelvic inflammatory disease
- Bartholinitis
- Proctitis
- Conjunctivitis
- Reactive arthritis
Clinical Manifestations: Women

- Majority - no signs or symptoms
- Cervicitis
  - Discharge, ectopy, edema, induced bleeding
  - 30-50% have mucopurulent cervicitis (>30 PMNs per oil immersion field)
- Pelvic Inflammatory Disease (PID)
- Ectopic Pregnancy
- Infertility
Chlamydia Adhesions: Fitz-Hugh Syndrome
Pelvic Inflammatory Disease (PID)

• Diagnostic criteria- only ONE of the following:
  – Cervical motion tenderness
  – Uterine tenderness
  – Adnexal tenderness

• Hospitalize
  – Pregnant
  – Tubo-ovarian abscess
  – Appendicitis cannot be excluded
  – Did not respond to PO antibiotics
  – Patient has nausea and vomiting, or high fevers/severe illness
  – Unreliable follow-up if treated as outpatient
Pelvic Inflammatory Disease (PID)

- Inflammation of upper genital tract
- May include endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis
- STDs involved: GC, CT, Gardnerella vaginalis, Mycoplasma hominis, Ureaplasma urealyticum; anaerobes, enteric Gram-negative rods
- Most common cause of gynecologic visits to US emergency departments
- Adolescents and young adults at high risk
Lymphogranuloma venereum (LGV)

- *Chlamydia trachomatis* serovars L1-L3
- Unilateral painful inguinal lymphadenopathy; “groove sign”; initial ulcer is short-lived
- Rectal exposure leads to proctocolitis
- Dx: culture, immunofluorescence, or nucleic acid detection
- Rx: Doxycycline 100mg po BID X 21d
Who to Test for Chlamydia?
U.S. Preventive Services Task Force Guidelines

- Women with mucopurulent cervicitis or PID (diagnostic testing)
- All sexually active women ≤ 24 years old
- Annual testing for CT of all women ‘at risk’, defined very liberally (prior CT or any other STI; inconsistent condom use; new or multiple partners; exchange sex for money or drugs)

http://www.uspreventiveservicestaskforce.org/uspstf07/chlamydia
Chlamydia trachomatis treatment

• Duration of therapy depends on serotype:
  – **Azithromycin** 1g PO X 1d **OR**
  – **Doxycycline** 100mg po BID X 7d
  – L1-L3 serotypes: Doxycycline 100 mg PO BID X 3 weeks **OR** Azithromycin 1g PO q week X 3 weeks

• *Test-of-cure* (repeat testing 3–4 weeks after completing therapy) is not routinely recommended

• Providers also are strongly encouraged to retest all women treated for chlamydia infection whenever they next seek medical care within the following 3–12 months (*Reinfection* rates are high!)
Gonorrhea vs Chlamydia: Clinical Presentation
• **Gonorrhea**

  – Case rate is highest of any industrialized country; 50x that of Sweden; 8x Canada.

  – After declining steadily to 1996, rates level for 15 years, but now increasing last 3 years.

  – For last decade cases have doubled in MSM

  – Antibiotic resistance increasing
In 2016, a total of 468,514 cases of gonorrhea were reported in the US.
Gonorrhea — Rates of Reported Cases by Sex, United States, 2007–2016

- 18.5% increase during 2016. 145.8 cases/100,000
- 13.8% increase in women, 22.2% increase in men
Gonorrhea — Rates of Reported Cases by Age and Sex, United States, 2016

Men

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Rate (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>4.7</td>
</tr>
<tr>
<td>15-19</td>
<td>280.8</td>
</tr>
<tr>
<td>20-24</td>
<td>545.1</td>
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<tr>
<td>25-29</td>
<td>350.7</td>
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<tr>
<td>30-34</td>
<td>233.4</td>
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<tr>
<td>35-39</td>
<td>140.7</td>
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<tr>
<td>40-44</td>
<td>92.8</td>
</tr>
<tr>
<td>45-54</td>
<td>35.2</td>
</tr>
<tr>
<td>55-64</td>
<td>6.7</td>
</tr>
<tr>
<td>65+</td>
<td>170.7</td>
</tr>
<tr>
<td>Total</td>
<td>170.7</td>
</tr>
</tbody>
</table>

Women

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Rate (per 100,000 population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>19.1</td>
</tr>
<tr>
<td>15-19</td>
<td>482.1</td>
</tr>
<tr>
<td>20-24</td>
<td>595.5</td>
</tr>
<tr>
<td>25-29</td>
<td>351.8</td>
</tr>
<tr>
<td>30-34</td>
<td>179.0</td>
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<tr>
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<td>5.6</td>
</tr>
<tr>
<td>65+</td>
<td>0.7</td>
</tr>
<tr>
<td>Total</td>
<td>121.0</td>
</tr>
</tbody>
</table>
Gonorrhea — Rates of Reported Gonorrhea by MSM\(^\dagger\), MSW\(^\dagger\), and Women, STD Surveillance Network (SSuN)\(^\ddagger\), 2010–2015

STIs Will Occur for Persons Using PrEP

- Analysis of HIV/STI incidence in PrEP users in large healthcare system (Kaiser Permanente San Francisco) from 2012 to 2015

PROUD: similar rates of any STI in 12 mos before starting PrEP (63%) vs during 12 months of PrEP (57%)[2]

Drug-Resistant Gonorrhea

- 1940s: Sulfonamides
- 1950s: Penicillins
- 1960s: Tetracyclines
- 1990s-2000s: Fluoroquinolones
- 2010s: Azithromycin and cephalosporins
Neisseria gonorrhoeae — Distribution of Isolates with Penicillin, Tetracycline, and/or Ciprofloxacin Resistance, 2016

NOTE: PenR = penicillinase-producing Neisseria gonorrhoeae and chromosomally-mediated penicillin-resistant N. gonorrhoeae; TetR = chromosomally- and plasmid-mediated tetracycline-resistant N. gonorrhoeae; and QRNG = quinolone-resistant N. gonorrhoeae.
Percentage of GISP Isolates with Reduced Azithromycin Susceptibility (MICs ≥2 µg/ml) — 2006–2015*

2.6%
CDC Treatment Recommendations for Gonorrhea

• **First-Line (preferred)**
  – Ceftriaxone 250 mg IM X1 + Azithromycin 1g PO X 1
  – Even if *C. trachomatis* is ruled out!

• **Alternate (non-preferred):**
  – Cefixime 400mg IM X1 + Azithromycin 1g PO X1*

If a patient experiences cefixime treatment failure:
  – Re-treat with 250 mg ceftriaxone intramuscularly and 2g azithromycin orally
  – Return for tests-of-cure within 2 weeks, preferably with culture, or, if culture is not available, with NAAT. If the follow-up NAAT result is positive, a specimen for culture should be obtained

*MMWR June 5, 2015;64(RR3):1-137*  
**CDC STD Guidelines 2015**
Spreading Resistance

• CDC press release
  – A cluster of GC infections in Hawaii with decreased ceftriaxone susceptibility and high level resistance to azithromycin.
## GC Drugs in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solithromycin</td>
<td>Fluoroketolide</td>
<td>Phase II: 100% efficacy for genital, oral, and rectal; Phase III ongoing;</td>
</tr>
<tr>
<td>Zoliflodacin</td>
<td>Spiropyrimidinetrione topoisomerase inhibitor</td>
<td>Phase II showed high efficacy against urogenital infections; 98%-100% cure rate; in vitro activity against FQ-resistant and macrolide-resistant strains</td>
</tr>
<tr>
<td>Gepotidacin</td>
<td>Triazaacenaphthylene topoisomerase inhibitor</td>
<td>Phase II trial with &gt;95% cure rates; in vitro activity against FQ-resistant and macrolide-resistant strains</td>
</tr>
</tbody>
</table>

Hook 2015 CID; Alirol 2017 PLOS Medicine; clinicaltrials.gov NCT02257918 and NCT02294682
AND
When the antibiotics well runs dry....
58 y/o man R eye pain and redness X 4 days
- No medical care X 20 years
- No sex in the past 4 years
- Right eye: Panuveitis
- Serum CIA reactive; RPR 1:128
Patient with hearing loss

36 year old gay man with sudden onset of fluctuating bilateral hearing loss and tinnitus

- Sensorineural with poor word discrimination
- Diffuse maculopapular rash on trunk sparing palms and soles
- Serum CIA reactive; RPR 1:2048
Treponema pallidum

He who knows syphilis knows medicine

~ William Osler
Syphilis

- Primary infection (painless ulcer or chancre at the infection site - heaped-up border with clean base)
- Secondary infection (skin rash-palms and soles, mucocutaneous lesions, and lymphadenopathy)
- Tertiary infection (cardiac, gummatous, or neurological lesions)
Secondary Syphilis

* 36 states were able to classify ≥70% of reported cases of primary and secondary syphilis as either MSM†, MSW†, or women for each year during 2012–2016.

† MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.
US Primary and Secondary Syphilis

17.6% increase 2016! 14.7% increase in men; 35.7% increase in women
STDs accelerating among men, particularly gay and bisexual men

Men accounted for more than **89 percent** (24,724) of all primary and secondary syphilis cases in 2016.

Rates increased among men by **15 percent** – from 14 cases per 100,000 men in 2015 to 16 per 100,000 men in 2016.

**From 2015 to 2016, rates of syphilis increased:**

**Among women**
- By 36 percent
- From 1 case per 100,000 women in 2015 to 2 per 100,000 women in 2016

**Among newborns** (congenital syphilis)
- By 28 percent
- From 12 cases per 100,000 live births in 2015 to 16 per 100,000 live births in 2016

* CS = Congenital syphilis; P&S = Primary and secondary syphilis.
Syphilis therapy

• Early stages (primary, secondary, early latent)
  – 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
• Late latent/unknown duration
  – 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks
• Neurosyphilis
  – Aqueous penicillin 18 to 24 MU IV X 10-14 days
  – Procaine penicillin 2.4 MU IM + probenecid 500 mg po QID X 10-14 days
  – Ceftriaxone 1-2g IV/IM X 10-14 days
• Jarisch-Herxheimer: within 6 hours after therapy of early syphilis; antipyretics only; may induce early labor
What stage(s) of syphilis involves the eye?
What part(s) of the eye is/are involved?

- **Every** part of the eye can be involved during any stage of the infection.

- Majority of eye manifestations associated with syphilis are also associated with many other infectious and non-infectious diseases.

AJO 1930; 13:285-294
Ocular Syphilis

**Manifestations:**
- Conjunctivitis, scleritis, and episcleritis
- **Uveitis:** anterior and/or posterior
- Elevated intraocular pressure
- **Chorioretinitis,** retinitis
- Vasculitis

**Symptoms:**
- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness

**Diagnosis:**
- Ophthalmologic exam
- Serologies: RPR, treponemal tests
- Lumbar puncture

The lumbar puncture in this patient was abnormal. What should you treat him with?

A. BPG 2.4 MU X 1
B. BPG 2.4 MU X 3 doses one week apart
C. Aqueous Penicillin G 24 MU per day X 10 days
D. Prednisone 60mg PO daily X 10 days
Patient with hearing loss

- IV aqueous crystalline penicillin G 4,000,000 units IV q 4 hours + steroids X 10 days
- JH reaction after 1st dose of penicillin
- Complete resolution of symptoms 1 month after therapy
Otosyphilis

- **Diagnostic criteria**: cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Diagnosis is presumptive; **CSF examination is normal in 90% of cases**
- **Therapy**: IV penicillin (+ corticosteroids)
- **Prognosis**: 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo
  - Absence of hearing fluctuations, longer duration of symptoms, and age >60 years are bad prognostic indicators
STRATEGIES AND APPROACHES FOR STD PREVENTION AND CONTROL
STD Prevention and Control Strategies

- Prevent
  - Health Education and Promotion
  - Behavioral Interventions
  - Vaccination (HBV and HPV)
- Detect and Link to Care
  - Screening of Asymptomatic Persons
  - Diagnosis of Symptomatic Persons
- Treatment and Follow up
- Case--Partner management and counseling
Public Health Interventions to Increase Screening

- Clinical Settings
- Community outreach
  - Mobile vans
  - Venue-based- pharmacies, bars, health fairs, hairs salons etc
  - Field-based through contact tracing programs

- Online internet or smart phone outreach
  - I Want The Kit
  - Internet sites offering STD testing
    - Order online, mail self-collected specimen, test in lab
    - Order online, collect and test at home, instant results
  - E-STD Services for STD diagnosis and treatment
    - E-testing and e-prescriptions
    - For patients and partners
“ASSURED” Criteria for POC

**A**ffordable: by those at risk of infection

**S**ensitive: few false negatives

**S**pecific: few false positives

**U**ser-friendly and simple to perform: 3-4 steps, minimal training

**R**apid and Robust

  - rapid: enable treatment at first visit
  - robust: no refrigerated storage

**E**quipment-free: easily collected non-invasive specimens

**D**elivered: delivered to end-users

http://www.who.int/std_diagnostics/about_SDI/priorities.htm
SD BIOLINE HIV/Syphilis Duo Rapid Test (Alere, Waltham, MA, USA; Standard Diagnostics, Yongin, South Korea)

DPP HIV-Syphilis Assay (Chembio Diagnostic Systems, Medford, MA, USA)

Multiplo Rapid TP/HIV Antibody Test (MedMira, Halifax, Canada)

INSTI HIV/Syphilis Multiplex Test (bioLytical Laboratories, Richmond, Canada)

mChip Assay (Junco Labs, Columbia University, New York, NY, USA; in collaboration with OPKO Health, Miami, FL, USA)

2013

2014

2015

2017

Disposable

Device
Acknowledgements

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  – Charlotte Gaydos, DrPH
  – Jonathan Zenilman, MD
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